diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhus, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, and

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza*, hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania*, cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

152. The kit of claim 16 in which at least one immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhu, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, and

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza*, hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania*, cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

REMARKS

1. General Matters

1.1. Claims 106-140, which were added by the amendment of 12/19/2000, were renumbered by the Examiner as 109-143, according

to 37 CFR 1.126 (see MPEP 608.01[j]). We therefore assume that claims 102-108 correspond to those claims as presented in the September 7, 1999 Supplemental Amendment After Final Rejection.[1]

Pending claims are 5, 6, 8, 10, 11, 16, 19, 27-30, 32-41, 43, 44, 46, 49-52, 55-57 and 59-143. Claims 6, 32, 33, 56-57, 101, 103, 106, and 128-143 are drawn to methods; claims 5, 8, 10, 11, 16, 27-30, 34-41, 43, 44, 46, 49-52, 55, 59-100, 102, 104, 105, and 107-127 are drawn to kits. Claim 19 is drawn to an immunogenic agent.

The following claims were not rejected for lack of written description/new matter: 19, 27-29, 33-37, 39-41, 43, 44, 46, 50-52, 66-71, 73, 102-143.

The following claims were not rejected for lack of enablement: 102, 104, 105, 107-127.

The following claims were not rejected on prior art grounds: 56, 57, 68, 69, 74, 75, 80-89, 94, 95, 101, 103, 106, 128-143.

The following claims were rejected, on one or more grounds, but are not listed on page 2 as pending: 9 (see OA §§5, 7) and 47 (see OA §§7, 10, 11, 12).

By this amendment, claims 89, 69, 70, 75, and 76 are cancelled, claims 5, 19, 30, 32, 38, 40, 56, 67, 71, 73, 77 and 129 are amended, and claims 144-152 are added.

New claim 144 combines the limitations of original claim 32 (preliminary amendment of February 12, 1996)[2] with those of IPE claim 5:

> The use of claim 20 wherein an immunogen other than a BCG, diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B,

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[1] We also assume that the substitute paper filed May 1, 2000 (presenting a "reduced" set, just claims 102-105) was disregarded in view of the entry of the September 7, 1999 paper. With the latter entered, we do not want the substitute paper entered; it would be redundant.

[2] With certain previously accepted amendments.

> hemophilus influenza, measles, mumps and rubella, influenza, cholera, BCG, plague, neumococcus, neisseria, varicela, rabies, typhoid and yellow fever immunogen is administered.

New claim 145 similarly combines the limitations of original claim 32 with one of the alternative embodiments of IPE claim 21:

> The use of claim 20 wherein the mammal has already received at least one, preferably two, more preferably at least three, and most preferably at least four, dosings of said immunogen prior to administration of said composition.

IPE claim 20 had recited

> Use of an immunogen in the manufacture of a composition to prophylactically or therapeutically reduce the incidence or severity of a chronic immune-mediated disorder in a mammal which, at the time of first administration of said immunogen, is less than 42 days of age.

New claim 146 similarly combines the limitations of original claim 32 with those of IPE claim 6:

> The use of claim 20, wherein for at least one such immunogen, the total dosage during the first 112 days after birth is substantially greater than that required for immunization against the infectious disease.

New claim 147 similarly combines the limitations of claim 32 with those of IPE claim 29 and IPE claim 22.

Claim 148 is a method claim, based on claim 32, but with the maturation limitation of kit claim 102.

Claims 149-152 are rewrites of claims 69, 75, 70 and 76.

1.2. The examiner continues to object (OA §3) to claims 5, 6, 19, 30, 32, 56-68, 69-71, 73 and 75-77, for "informalities in punctuation and nomenclature". The only specifically noted informality is in claim 70, line 3, where, as requested, we have

inserted a comma between "diphtheria" and "tetanus".

The original objection (June 20, 2000, §4) to these claims stated:

> The nomenclature used to recite the immunogens in the present claims is inconsistent. All claims should either be amended to recite the immunogen by the name of the etiologic agent, or by adding the term "vaccines" after the listing of disease names. Furthermore, bacterial names are conventionally written listing genus and species either in italics of underlined with the genus name capitalized. Also, the complete virus names of the viral immunogens should be recited. For example, "varicella" should be amended to varicella-zoster virus. Finally, all claims should be reviewed for punctuation, as commas are absent between some of the immunogens (see claim 19, line 11, "dengue toxoplasmosis" (for example).

The Examiner now adds

> Applicant's arguments regarding the nomenclature have been fully considered but they are not persuasive. Applicant argues that when a disease name is recited, it is applicant's deliberate intent to cover any immunogen of any etiologic agent which causes that disease. Applicant's claims, however, do not recite "plaque" immunogen, for example. They simply recite "plague". "Plague" is the name of a disease, not an immunogen. The metes and bounds of the claimed immunogen(s) simply cannot be determined if the claim fails to recite it (them). Similarly, "pertussis" is the name of a disease, not an etiologic agent ad "varicella" is the name of a disease, not an immunogen.

The Examiner says that the claims do not recite a "plague immunogen", just "plague". We disagree. Claim 19 recites "plague...immunogens". Clearly, "plague" is an adjective qualifying "immunogens".

We have studied the claim terminology in detail. Referring first to claim 5, we have:

BCG	Bacillus Calmette Guerin, an attenuated form of Mycobacterium bovis, used as a tuberculosis vaccine
diphtheria	disease caused by Corynebacterium diphtheriae
tetanus	disease caused by Clostridium tetanii
pertussis	disease caused by Bordetella pertussis
polio	disease caused by polio virus
hepatitis A	disease caused by A strain of hepatitis virus
hepatitis B	disease caused by B strain of hepatitis virus
hemophilus influenza	species of microorganism
measles	disease caused by measles virus
mumps	disease caused by mumps virus (a paramyxovirus)
rubella	German measles, disease caused by rubella virus
influenza	disease caused by influenza virus
cholera	disease caused by Vibrio cholerae
plague	disease caused by Yersinia pestis
pneumococous	alternate name for Streptococcus pneumoniae, commonest cause of lobar pneumonia
neisseria	genus of microorganisms including the pathogens N. meningitidis (causing meningitis) and N. gonorrhoeae (causing gonorrhea)
varicella	chicken pox, caused by chicken pox virus
rabies	disease caused by rabies virus
typhoid	disease caused by Salmonella typhi

yellow fever	disease caused by yellow fever virus

Claim 70 additionally recites

encephalitis	disease with multiple causes, including HSV-1, varicella-zoster virus, Epstein-Barr virus, togaviruses, arenaviruses, and adenoviruses
meningococcal	pertaining to Neisseria meningitidis
meningitis	disease with multiple causes, including enteroviruses, influenza viruses, para influenza viruses, mumps virus, HSV-1 and HSV-2
pneumonia	disease with multiple causes, incl. Chlamydia pneumoniae, Legionella spp., Pseudomonas spp., Klebsiella pneumoniae, Nocardia spp., Mycobacteria pneumoniae, rhinoviruses, hantaviruses, paramyxoviruses, coronaviruses, Candida spp., Aspergillus spp., Mucor spp., and Pneumocytis carinii.
typhus	disease caused by Rickettsia prowazekii
typhoid fever	alt. name for typhoid, see claim 5
streptococcus	a genus of bacteria, incl. S. mutans (causes caries) and S. pneumoniae (causes pneumonia)
staphylococcus	a genus of bacteria
lyme disease	disease caused by Bordetella burgdorferi
E. coli	a species of bacteria
shigella	genus of bacteria, incl. S. dysenteriae, S. flexneri, S. boydii, S. sonnei
leishmania	a genus of parasitic protozoa which cause leishmaniasis
leprosy	disease caused by Mycobacteria leprae
cytomegalovirus (CMV)	a virus
respiratory syncytial virus	a virus

Epstein Barr virus	a virus
herpes	disease caused by herpes virus
parainfluenza	disease caused by a virus of the parainfluenza virus group
rotavirus	a group of viruses
adenovirus	a group of viruses
human immunodeficiency virus (HIV)	a virus
nonA, nonB hepatitis	disease caused by a nonA, nonB, strain of hepatitis virus
Japanese encephalitis	a form of encephalitis
flavivirus	a group of viruses, incl. the yellow fever virus
dengue	disease caused by dengue virus
toxoplasmosis	disease caused by Toxoplasma gondii
coccidiomycosis	disease caused by Coccidiodes immitis
schistosomiasis	disease caused by Schistosoma spp., e.g., S. mansoni, S. japonicum, and S. haematobium
malaria	disease caused by Plasmodium spp., e.g., P. falciparum, P. vivax, P. ovale, P. malariae
anthrax	disease caused by Bacillus anthracis

Claim 71 additionally recites "smallpox", which is a disease caused by the smallpox virus.

We have amended claims 5, 30, 32, 56, 67, 73 and 77 to separately group immunogens identified directly by source organism from those identified by indirectly by the disease which their organism causes. With regard to identification by source organism, we believe that it is perfectly acceptable in scientific practice to identify a genus of organisms (e.g.,

"Neisseria", "Shigella") rather than a particular species.

In the case of claims 69 and 75, a similar goal was accomplished by cancelling those claims and replacing them with new claims 149 and 150, respectively. We have dropped reference to "Japanese encephalitis" as it is included in "encephalitis", and to "yellow fever virus" as it is included in "flavivirus".

Likewise, in the case of claims 70 and 76, these have been cancelled and replaced by new claims 151 and 152.

The markush group was deleted from claim 19.

2. Definiteness (OA §4)

2.1. The Examiner previously questioned the antecedent basis the "after birth" limitations in claims 6, 57, 11 and 38:

> Claim 6 is indefinite as lacking clear antecedent basis. Claim 6 recites "wherein for at least one such immunogen, the total dosage during the first 112 days after birth...". Claims 6 depends from claim 32, which recites dosages during the first month or prior to 42 days after birth, not 112 days. Claim 57 is also indefinite for the same reason; claim 57 depends from claim 56, which also recites dosages during the first month or prior to 42 days after birth.

We asked the Examiner to clarify how this was to be corrected:

> We realize that in dependent claims, one normally cannot recite "the X" unless "a/an X" has already been recited. However, to apply that rule to "during the first 112 days after birth" seems frivolous. Should we amend claim 32 to recite "during a period which is from birth to a time 112 days after birth"? Or, "where the animal is alive 112 days after birth, where during the first 112 days after birth"? Or is the Examiner looking for something else?

The Examiner has not responded with any suggested language. The new rejection was applied to claim 11 and 38, but not to 6

and 57. Does that mean that 6 and 57 are fine, after all, or that they were overlooked?

While the Examiner maintains that the "antecedent basis of claims 11 and 38 is not clear", that is not enough to justify an indefiniteness rejection. MPEP §2173.05(e) says that "the failure to provide an explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite.... Inherent components of elements recited have antecedent basis in the recitation of the components themselves". The date of birth of a person is inherent to that person.

Reviewing the original rejection, we think that we may have misunderstood the Examiner's reasoning. We thought that the concern was with the word "the" before "first 112 days after birth". However, it may be that the Examiner simply thought that there was an inconsistency between reciting the "first 112 days after birth" in claim 6 and "prior to 42 days after birth" in base claim 32. If so, we can readily resolve the issue.

Claim 32 requires that for at least one immunogen, the <u>first dose</u> of the immunization schedule be administered when the mammal was "less than 42 days old, measured from both".

Claim 6 required that for at least one immunogen, the <u>total dose</u> administered under the schedule during the first 112 days after birth be substantially greater than that required for immunization against the corresponding infectious disease.

This language is readily harmonized. On page 32, Applicant presents several conventional immunization schedules, with DTP given at weeks 6, 10 and 14. Thus, there are 3 DTP doses in the first 112 days (16 weeks) after birth, and this is presumably all that is required for immunization against these diseases. On page 107, several preferred immunization schedules are given. In schedule 1, the first DTP dose is given in week 0, so the

"first dose less than 42 days after birth" requirement of claim 32 is plainly satisfied. DTP is given in weeks 0, 2, 4, 6, 8, 10, 12 and 14, a total of 8 doses in the first 112 days after birth. Even if we ignored the last dose, the total dose plainly exceeds that required for protection against diphtheria, tetanus and pertussis, see page 32, and hence satisfies claim 6.

Similar arguments may be made concerning claims 11, 38 and 57.

2.2. We have deleted "substantially" from claim 38.

2.3. Attacking "less than 28 days" (claim 40) the Examiner has questioned applicant's position that a claim may state an upper limit without also stating a lower limit. The Examiner's attention is respectfully directed to MPEP §2173.05(c)(II), page 2100-149, col. 2:

> In a claim directed to a chemical reaction process, a limitation required that the amount of one ingredient in the reaction mixture should "be maintained at less than 7 mole percent" based on the amount of another ingredient. The examiner argued that the claim was indefinite because the limitation sets only a maximum amount and is inclusive of substantially no ingredient resulting in termination of any reaction. The court did not agree because the claim was clearly directed to a reaction process which did not warrant distorting the overall meaning of the claim to preclude performing the claimed process. In re Kirsch, 498 F.2d 1389, 182 USPQ 286 (CCPA 1974).

However, in the particular case of claim 40, in view of the definition of "dose" at page 26, lines 8-11, we have amended claim 40 to recite "<u>at least one and</u> less than 28 days".

2.4. The Examiner asserts that the members of the recited Markus groups are not members of a recognized class because some members are "diseases" and others are "immunogens".

In fact, all of the members are "immunogens", whose source

organisms were identified either directly or by reference to the diseases which they cause (and with which the immunogens in question are thereby associated). For some diseases, there is only one known pathogen, and for others, there are several. The common properties relating all of the immunogens are (1) they are immunogenic in mammals, and (2) they are mammalian pathogen-associated.

In answer to the Examiner's question, if several different organisms cause a recited disease D, then any immunogen associated with any of these organisms is contemplated as "D" immunogen.

Since herpes viruses are an art-recognized taxonomic group, and "herpes" is an art-recognized disease, it follows that reference to "immunogens of an organism causing herpes" is definite.

2.5. In claim 19, the Examiner criticizes the term "a molecule that cross-reacts immunologically to at least one of said immunogens" because it is unclear whether it is based on eliciting any immune response. This is moot in view of the amendment of 19.

3. Description/New Matter (OA §5)

Technically speaking, if new matter is allegedly added to a claim, the rejection is properly termed a rejection for "lack of written description", not a rejection for "new matter". See MPEP §2163.06(I).

3.1. With respect to the label warning of claim 59, the Examiner says that there is no reference to warning labels or instructions per se at pp. 51-52, p. 7, l. 11-14, or p. 54, l. 14-21.

Page 7, lines 11-14 states

> The lack of concern over the ability of vaccines to induce a chronic immune mediated disorder (e.g., but not limited to,

> diabetes) is further evidenced by the lack of warnings on package inserts and labels of such products about such diseases.

Thus, the specification explicitly criticizes the prior art vaccine labeling for failing to warn about the ability of vaccines to induce a chronic immune-mediated disorder.

FDA practice requires one to place warnings on a package insert if there is a potential adverse event, and this is well known to those skilled in the art. See, e.g., 21 CFR 201.57(e).

As the Examiner is well aware, it is not necessary that the exact language of the claim appear in the specification in order to satisfy the "description" requirement. In re Lukach, 169 USPQ 795, 796 (CCPA 1971); In re Edwards, 196 USPQ 465 (CCPA 1978); In re Smythe, 178 USPQ 279 (CCPA 1973) ("fluid" described by "gas"). The specification is directed to a person skilled in the art, who therefore would be aware of FDA labeling requirements.

Page 54, lines 14-21 contemplates screening standard immunization schedules for the ability to "induce and/or enhance the incidence and/or severity of at least one chronic immune-mediated disorder". Suppose that such a screen were positive. If so, then under the food and drug laws, it would be necessary to mention this adverse effect in the labeling. See Appellant's Brief, pp. 9-10.

Page 51, lines 26-28 teaches that the kits will be "in forms suitable for pharmacological administration". Arguably, if an immunogen were screened per page 54, and found to cause diabetes under the contemplated immunization schedule, the FDA would require a warning on the labeling and a kit without such labeling would not be "suitable for pharmaceutical administration". See the December 19 amendment.

Original claim 2, which is part of the "description", stated:

> The method of claim 1 where said mammal is

> not immunized with an immunogen in such amounts and at such times as would substantially induce an immune-mediated disorder.

Since manufacturers of vaccines have no control of how the vaccines are used by physician-purchasers, a label warning is plainly a contemplated means of accomplishing what is suggested by original claim 2.

3.2. Before addressing the merits of the rejection of claim 32, we wish to reiterate that we would be willing to cancel this claim as part of an agreement under which our "kit" claims were allowed. Also, we would consider replacing claim 32 with certain new claims (144-147).

The questioned limitations of claim 32 are:

(1) if only one immunogen is administered, it is other than BCG;

(2) if the one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month; and

With regard to the "other than BCG" limitation, (1) above, the limitation appears to be intended to excise prior art like that of Grange and Stanford (1990) cited at page 6, lines 11-14, and Harada (1990), cited at page 9, line 16 to page 10, line 4, and hence "described" by page 31, lines 9-18. Moreover, original PCT[3] claim 1 (which automatically has "description") recited "said one or more immunogens... optionally including at least one

[3] This application is the national stage of PCT/US94/08825. This PCT application originally presented 24 claims. In IPE, original claims 1, 3, 4, 7, 12, 13, 18, 23 and 24 were deleted, and 25-30 were added. On national stage entry, a preliminary amendment cancelled 20 and 22 and added 31-33.

immunogen other than BCG". See also original PCT claims 5 ("other than BCG,... yellow fever", total of 21 immunogens listed) and claim 7 ("other than BCG...also...other than smallpox").

Limitation (2) was introduced to avoid any possibility of inherent anticipation by Adams (1947) (of record), as cited in Table 5 of Halsey (of record). Excission of a prior art species from a generic claim is proper, see In re Johnson, 194 USPQ 187 (CCPA 1977) and indeed was contemplated as a possibility, see page 31, lines 9-18. The Halsey article is cited in the specification (p. 109) and incorporated by reference, as are all articles (including Adams) cited by Halsey. See pp. 99-100. Hence, there is no violation of the "description" requirement.

3.3. The comment at the bottom of page 6 is moot as claim 89 has been cancelled.

4. Enablement/Utility Issues (OA §6)

4.1. With regard to enablement vs. utility (OA page 8, lines 6-9), in our view, when the Examiner questions the believability of a utility, she is making a utility rejection, while when the Examiner questions the quality of the written disclosure of a believable utility, she is making an enablement rejection. See MPEP 2164.07. Hence, the examiner questions extrapolation of animal data, which is a typical utility issue, see MPEP 2107.02 (III). In other words, this is a utility rejection in enablement rejection clothing, and the utility guidelines should apply. Hence, procedurally, these utility issues should be raised in a combined 101/112 ¶1 rejection, and any pure enablement issues in a separate 112 ¶1 rejection, see MPEP 2164.07.

4.2. As previously noted, claims 102, 104, 105 and 107-127 were not rejected for lack of enablement.

These claims have the following differentiating features:

102: similar to 59, but "the first dose of an immunogen to be given before the subject's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days in a mouse or rat".

104: Kit of 27 where the mammal is human and the disorder is an autoimmune disease.

105: Like 104, but dependent on the kit of 59.

107-108: Container label indicates identity and amount of each immunogen (dep. on 27/59).

109: labeling rehumans with family history of CIMD (dep. on 16, which requires humans, and is dependent on 59).

110-115: none of the immunogens are live vaccines (dep on 16, 72, 74, 75, 76 or 77. Claims 72, 74-77 require certain immunogens).

116: protection against 2 different infectious diseases, each with a different immunogen (dep on 16).

117: at least one pediatric and at least one non-pediatric immunogen (dep. on 16).

118: at least one immunogen given on or after 42 days after birth (dep on 16).

119: first administration before 28 days old (dep on 16).

120: first administration before 42 days old (dep on 16).

121: at least one P, D, T, Polio, HepB or HiB immunogen (dep on 16).

122: immunogens are not live vaccines (dep on 66-71).

123: Like 121 but dep on 43, and also listing BCG. Claim 43 requires that mammal is human, and is dependent on 27).

124: Like 123, but does not list BCG.

125: Like 116, but dep on 43.

126: Like 117, but dep on 43.

127: Disorder is one which develops at least one year after a vaccination (dep on 59, 60, 61, 62, 96, 97, 30, 49, 55, 74, 76, 77, 89, 91, 92, 98-100 or 106-117).

Inconsistently, some claims dependent on a claim not rejected for lack of enablement are themselves so rejected; namely, 131-136, which are dependent, directly or indirectly, on 127.

It should be noted that if, in the next action, the Examiner chooses to reject the aforementioned claims for lack of enablement, the new action cannot be made "final", as claims 131-6 could have been so rejected in this action.

Also, many of the claims not rejected for lack of enablement either require immunization of humans themselves (104) or are dependent on 16 or 43 and therefore incorporate that limitation (109-127). This suggests that limiting the main claims to humans would be a step toward overcoming the enablement rejection. Yet, at pages 8-9 of the office action, the Examiner says, "in the present case, the extrapolation of data based on a mouse model to humans and other mammals is questionable because of the criticality of the age of administration of the immunogen and the differences in maturation rates between rodents and humans".

Kit claim 102, which was not rejected for enablement, responds directly to that argument. So does new method claim 148.

Nonetheless, we have not made all claims directly or indirectly dependent on claims 102 and 148 because we do not regard the "maturation" limitation to be necessary. Our conclusions regarding the timing of the first administration are based, not just on data from animal models, but also on human epidemiology, e.g.:

Favorable	Unfavorable
BCG before 2 months	Pertussis, BCG at school age
smallpox at birth (P98, L18-22)	Pertussis, Hib, BCG at 3 months and at school age
	Hib or meningal polysaccharide at 3 months to 5 years (P93, L15-18)

See pp. 89-106 of the specification.

This data suggest that drawing the line at 42 days (~1.5 months) in human immunization is not unreasonable.

More generally, we believe that the disclosure is properly considered to satisfy the "how to use" disclosure requirements in view of (1) epidemiological data, (2) our animal studies, and (3) reports of vaccines causing human CIMD.

With regard to (1), the Examiner says that "epidemiological data alone does not establish a causal relationship". That is true, but it can render a proposed utility believable.

The scientific community often must rely on epidemiological data to establish causation. It is unethical to perform a clinical trial with a suspected toxic substance in order to "prove" the substance is toxic. Therefore epidemiology data alone is suffice to establish casual relationship for practical purpose. For example no one has ever done a prospective study to establish that cigarettes cause disease. The establishment of a casual relationship between cigarettes and disease is based on epidemiology data. The same goes with almost all toxins, for example asbestos, carcinogenic chemicals, radiation, toxic chemicals.

With regard to (2), the examiner questions the extrapolation of data from mice to humans "because of the criticality of the age of administration of the immunogen and the differences in maturation rates between rodents and humans". We attempted to address that issue in newly entered September 7, 1999 claim 102, discussed in §9.2 of the last amendment.

In response to Elliot's cautions concerning extrapolating from mice to humans (OA page 9, lines 1-7), we submit a copy of Classen and Classen, "Clustering of cases of insulin-dependent diabetes (IDDM) occurring three year after Haemophilus influenza B (Hib) immunization support causal relationship between

immunization and IDDM". The mice (NOD) received hepatitis B vaccine (HepB) at days 3 and 28. The "vaccinated" group also received DTaP, Hib and inactivated polio vaccines at weeks 10, 16 and 22. The "control" mice received saline injections at weeks 10, 16 and 22 instead. The "vaccinated group" developed diabetes at a higher rate.

The NOD mice were compared with Finnish children receiving 0, 1 (~26 months) or 4 (3, 4, 6 and 18 months) of HBV, as well as, of course, the usual childhood vaccinations. The additional doses were associated with a higher incidence of diabetes.

Thus, vaccination of NOD mice at weeks 10, 16 and 22 (i.e, 2 to 5 months) has an effect similar to vaccination of humans at 3-18 months. Hence, the extrapolation of the age of administration seems supported by the data.

Moreover, Elliot's comments must be placed in context; NOD mice and BB rats are overwhelmingly popular as animal models of human diabetes. See pp. 39-40 of Appellant's Brief; for more detail, see Appendix 2 to the Amendment of March 25, 1999. Similarly, MRL-lpr mice are accepted animal models of SLE, see Appendix 1 to the March 25, 1999 amendment.

Finally, we direct the Examiner's attention to claim 102. This claim calls for a first dose to be given "before the subject's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days after birth in a mouse or rat", and is based on page 29, line 13-19 of the specification:

> The present invention therefore can include administration of the immunogens to humans when said humans' immune systems are in a state of maturation and responsiveness comparable to that of mice or rats at the times indicated above, in such circumstances as it would be less effective to administer those immunogens to humans at the same chronological ages as they were administered to mice or rats.

New claim 148 is a method claim based on claim 32 but reciting the maturation limitation of claim 102 in place of the simple 42 day limitation of claim 32.

With respect to (3), while it is true that the method claims are drawn to reducing, not causing, CIMDs, the cited references show that vaccine administration can affect the incidence or severity of CID. They then must be placed in the context of Applicant's experiments showing that timing determines whether the effect is beneficial or detrimental.

At page 9, the Examiner states:

> Regarding applicant's agreement that there are now a large number of reports indicating vaccines may cause chronic immune mediated disorders, exhibits 1E, 5G, 1A, 5H, 5E, and Classen references, applicant is reminded that the present methods are drawn to reducing the incidence or severity of chronic immune-mediated disorders, not the converse. Thus, the relevance of this line of argument is not apparent.

This is a "half-full" or "half-empty" argument. If conventional practice elevates the risk of CIMDs, changing that practice reduces it. One is the converse of the other. The specification contemplates: (1) altering the immunization schedule to reduce the risk of CIMD, and (2) giving warnings when the schedule cannot be changed (see page 7, lines 11-14 and page 59, lines 11-14). It also contemplates limiting conventional immunization to those at high risk for infection, see page 70, lines 12-16.

5. Double Patenting (OA §7-8)

The double patenting rejection has been applied to claims 2-14, 16-17, 19, 21, 23-25, 27-33, 34-47, 49-55, 56-57, and 101-143. It is proper only as to the method claims, i.e., 6, 32, 33,

56-57, 101, 103, 106 and 128-143.

The double patenting rejection is improper as it relates to the "kit" claims, as they were restricted out in the parent case, see 35 USC §121. After all other issues are disposed of, Applicants will either (a) file a terminal disclaimer, or (b) cancel the method claims.

6. Prior Art (OA §9-14)

6.1. The first issue is whether in the case of the kit claims, as rejected as anticipated by Madore (§7), Dengrove (§8), Halsey (§9), John (§10) and Onazono (§11), did the Examiner properly disregard the "labeling" limitation; more particularly, is there a "functional relationship" between the "labelling" ("printed matter") and the drug and its container ("substrate").

While, in a claim to a product, language of intended use is ignored, these kit claims require the presence of certain labeling. This is a tangible requirement, not a mere statement of intended use.

The labeling is what the PTO calls "printed matter". Printed matter may constitute an element of a patentable claim and be given patentable weight, if there is a sufficient functional relationship between the printed matter and its substrate. See In re Gulack, 217 USPQ 401 (Fed. Cir. 1983); In re Miller, 164 USPQ 46 (CCPA 1969). Here, the printed matter explains how to use the substrate (the immunogen) to achieve the desired result (reduction in the incidence or severity of a chronic immune-mediated disorder).[4]

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[4] The "printed matter" doctrine is closely allied with the old "mental steps" and later "mathematical algorithm" doctrines, and, in this regard, it is interesting to note that an invention applying the rules and instructions for a game ("Cricket") to an otherwise old dart machine was held to be potentially patentable because the algorithm was not a mathematical one. See Arachnid Inc. v. Medalist Mktg. Corp.,

The Examiner maintains the rejection of the kit claims as anticipated by Madore (§7), Dengrove (§8), Halsey (§9), John (§10) and Onazono (§11) on the ground that there allegedly is not functional relationship between the printed matter and its substrate, as required by In re Gulack, 217 USPQ 401 (Fed. Cir. 1983) and In re Muller, 164 USPQ 46 (CCPA 1969).

What is a "functional relationship"? Presumably, it implies that without the printed matter, the substrate would be **less capable** of performing its function.

In the case of In re Miller, claim 10 read as follows:

> A measuring device comprising: a spoon for measuring ingredients; and volume measuring indicia defined in a normal volumetric unit on said spoon of a selected ratio to but indicating a volume different from the actual volume of ingredients being added to and measured in said spoon by said indicia, and a legend attached to said spoon specifying said ratio.

The court's opinion reproduces two apparatus of this type. In Fig. 2, we see a measuring cup with the legend "ONE HALF RECIPE", and various volumetric indicia. The line marked "2 CUPS" actually corresponds to a volume of one cup, so, if a full recipe called for "2 cups", by filling to the line in question, one would actually be adding the amount appropriate for a half recipe. In Fig. 3, we see a set of measuring spoons with a "½ recipe" tag. Here, the spoon marked "1 teaspoon" has a true capacity of ½ teaspoon.

Were these indicia and legends to be removed, one would have cups and spoons worthless for accurate measurement. If just the legends were removed, one would have just a conventional looking (but inaccurate) measuring device or cup. The Court found that

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18 USPQ2d 1941 (W.D. Wash. 1991). The claimed instructions for use do not define a mathematical algorithm.

there was "a new and unobvious functional relationship between a measuring receptacle, volumetric indicia thereon indicating volume in a certain ratio to actual volume, and a legend indicating the ratio".

Similarly, in the instant kit claims, there is a new and unobvious relationship among "containers holding pharmaceutically acceptable doses of one or more immunogens" (which is like Miller's "receptacle") the "labeling" of the containers to indicate the identity and amount of each immunogen they contain (which is like Miller's "volumetric indicia")[5] and the "instructions" for use (which is like Miller's "legend").

The last of these points deserves particular emphasis. Miller's "legend" is an instruction for use. "One Half Recipe" is an instruction to the cook to use the cup or spoon se tin question when he or she wishes to prepare a "one half" recipe without recomputation of the required amount of each ingredient. Without the cook to interpret the legends and indicia, the cup and spoons do not perform any function. Their functionality resides in what they communicate to the cook. They do not help the receptacle hold more ingredients, or keep them fresher. They do not make the receptacle more watertight or airtight. Their relationship -- especially the legend's relationship -- to the receptacle is closely akin to the relationship exhibited by the printed matter in the instant kit claims to the immunogens of those claims.

In Gulack, the claim was to an educational device, which could take the form of a hat with a headband. Imprinted on the headband (the substrate) was a cyclic sequence of integers (the printed matter) obeying a particular mathematical rule. What was the functional relationship? According to the CCPA, the digits

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[5] While this is not explicit in claims 27 and 29, it is an FDA requirement. The Supplemental Amendment, if entered, would make this explicit.

-- the printed matter -- were "related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits... exploit[ing] the endless nature of the band". In contrast, in the prior art Wittcoff reference, there was printed matter on the band, as in (1) above, but the data items were independent rather than arranged in a particular sequence.

Here, the labeling establishes a sequence, albeit temporal rather than spatial, for the use of the immunogens of the kit. Bear in mind that this relationship is between the printed matter and the immunogens, which are a part of the overall "substrate". In Gulack, the distinguishing relationship was between one printed element and another printed element. Hence, the present case actually presents a stronger justification for the finding of a functional relationship than does Gulack.

While the immunogens are functional despite the labeling, that does not mean that a functional relationship is absent. Congress, in enacting the Food, Drug and Cosmetic Act (FDCA), recognized the existence of a functional relationship between a drug and its labeling. Thus, a new drug is not approved per se, rather it is approved for a particular indication (use). The new drug application includes "specimens of the labeling proposed to be used for such drug", see FDCA Sec. 505(b)1)(F). The FDA reviews the NDA and can refuse to approve if the testing was inadequate to show that "such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" (see FDCA Sec. 505(d)(1)) or the results "show that such drug is unsafe for use" or "do not show that such drug is safe for use" under "such conditions" (see FDCA Sec. 505(d)(2)). Moreover, approval may be refused if "such labeling is false or misleading in any particular" (see FDCA Sec. 505(d)(7)).

Once a new drug has been approved, that approval may be

withdrawn for the same reasons that approval could have been withheld in the first place. See FDCA Sec. 505(e).

Moreover, the FDCA draws a distinction, for all drugs, between adulteration and misbranding. If a drug contains a substance which is deletenous to health, it is adulterated. See FDCA Sec. 501. However, even a drug free of deletenous substances can be sanctioned if it is misbranded. A drug is misbranded if "its labeling is false and misleading in any particular", see FDCA Sec. 502(a). More significantly, it is misbranded "unless its labeling bears (1) adequate directions for use; and (2) such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." See FDCA Sec. 502(f). A possible loophole is closed by FDCA Sec. 502(j), which says that a drug is "misbranded" if it is "dangerous to health when used in the dosage manner, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof."

Prescription drugs dispensed by filling the prescription of a physician are exempt from Sec 505(f) and (j), cited above, but only if the drug bears a label presenting "the directions for use and cautionary statement, if any, contained in such prescription." FDCA Sec. 503(b)(2)

According to 21 CFR §201.57(e),

> Under this section heading, the labeling shall describe serious adverse reactions and **potential safety hazards, limitation in use imposed by them,** and steps that should be taken if they occur. **The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved**.

Plainly, FDA realizes that some manufacturers and this

consultants will argue their product has not been proven to cause a serious adverse event even though the data shows an association. FDA requires manufacturers to warn about a potential adverse event as soon as there is any reasonable evidence of an association. This is because it feels that the cost to the public of an unnecessary warning is much less than that of a delayed one.

While a physician may prescribe a drug for an off-label use without violating the FDCA, such prescription may be considered medical malpractice, and insurers may refuse to pay for such use.

We caution the Examiner against an overly restrictive definition of a "functional relationship", namely, that "without the printed indicia or numbers, the substrates lose their function." The case law does not justify that definition.

In Gulack the substrate was a headband. It remained functional as a headband, only its educational function would have been lost if the integer sequence were omitted. In Miller, the substrate was a measuring cup or spoon. It could still be used as a cup or spoon if the indicia were omitted. Thus, it is clear that neither case presented a substrate whose function was totally dependent on the indicia.

Here, it is true that the immunogen (if protective in its own right) could be used to protect against the corresponding infectious disease. However, without the claimed directions for use, the clinician would not know how to use it to limit the increased incidence or severity of the disorder attributable to late immunization.

In determining the functionality of an immunogen, it is appropriate to consider its side effects, not just its specific immunogen effect. If the side effects are detrimental, its functionality is reduced. If the side effects are beneficial, its functionality is enhanced.

The fact the immunogen has a residual level of

functionality, absent the indicia, does not mean that there is no functional relationship between the immunogen and the indicia (labeling). If the latter increases the functionality of the immunogen, the necessary relationship exists and it is proper to give patentable weight to the labeling limitation.

An interpretation of "functional relationship" as meaning necessary for the functioning of the substrate is inconsistent with the alternative holding of the Federal Circuit in In re Lowry, 32 USPQ 2d 1031 (Fed. Cir. 1994). Lowry claimed memory for storing data which comprised a particular data structure (a pyramidal and hierarchical arrangement of "attribute data objects", ADOs), a data processing system comprising a database, a CPU, and memory means for holding the claimed data structure and methods of manipulating ADOs. The Examiner rejected the memory claim under ' 101, the system claims as obvious, and the method claims as anticipated. The Board reversed the ' 101 rejection, and upheld the prior art rejections. According to the Board, Lowry's data structures were analogous to "printed matter" and lacked a "functional relationship" to the substrate (the memory).

On appeal, the Federal Circuit held that because Lowry's data structures upon storage in memory, cause electromagnetic changes, there is a physical change, albeit invisible to the eye, and hence the data structures are not analogous to "printed matter".

However, it continued that even assuming that the analogy is valid, the Board erred in its reliance on Gulack. It pointed out that the ADOs enabled "more efficient data processing operations on stored data" in particular, that they "facilitate addition, deletion and modification of information stored in memory". The memory, of course, has a "function" even without Lowry's data structure. Lowry's merely structures "provided increased efficiency". However, that qualified as a "functional

relationship": "In sum, the ADOs perform a function, Gulack requires no more".

We also think it worth reiterating that if the labeling is given patentable weight (as we think proper as a matter of law), it is clear that the claims are not anticipated or rendered obvious by the reference. While it is certainly normal for an immunogen to be labeled with directions for use, to immunize against an infectious disease, and with warnings of side effects like acute toxicity, applicant was the first to teach that it should be labeled to direct its administration so as to limit the increased incidence and severity of a chronic immune mediated disorder (e.g. diabetes).

Consistent with this analysis, the PTO has allowed claims with "labeling" limitations.

Gerbe, USP 3,627,122, SYSTEM AND APPARATUS FOR THE ADMINISTRATION OF DRUGS (1971), claims an apparatus comprising compartmented trays, with "a patient and dose identification card" covering the bottom of each compartment, the card "having a folded portion...for holding said card in place". The claim also recites that each compartment has "a longitudinal pocket in one wall for a signal identification card".

Phykitt, USP 5,687,841, COMBINATION SHIPPING CONTAINER, MIXING AND DRINKING VESSEL (1997) claims the combination of analgesic medications and a package which serves both a shipping container and a mixing vessel. Claims 21-22 recite

> 21. The combination, according to claim 1, wherein said package further includes at least one of indications, directions, warnings, drug interaction precautions, active ingredients information and storage information disposed on an outer surface of one of said back portion and said front portion of said package.
>
> 22. The combination, according to claim 21, wherein said package includes each of said

> indications, said directions, said warnings, said drug interaction precautions, said active ingredients information and said storage information disposed on said outer portion of said back portion of said package.

Robertson, USP 5,752,723, PHARMACY LABEL AND PRESCRIPTION DRUG DISPENSING (1988) claims (18) "a labeled prescription drug package comprising...indicia comprising the name of a prescription drug, the dosage for proper administration of the drug, and the quantity of the drug to be provided in a package, imaged on said first label section".

See also Olney, USP 5,011,853 (claim 18= "a label which indicates that said pharmaceutical agent can be used for reducing the neurotoxicity of at least one cholinergic neurotoxin"); Kelly, USP 5,208,031 (claim 4= "the packaging material indicates that the sexual lubricant mixture... can reduce the risk of being infected by at least one type of sexually transmitted virus"); Sanders USP 4,820,635 (claim 1= "A kit ...comprising... instructions for performing the assay").

This is the first of several points in the brief in which we cite prior patents as evidence that a particular claim is acceptable. while we agree with the PTO that such evidence is not conclusive -- it certainly could not justify a legal position which was plainly contrary to the patent statute -- we cannot agree that is legally irrelevant. The courts have repeatedly found such evidence to be probative. Of course, the greater the number of patents cited, the more weight they carry. And the examiner is welcome to attempt to rebut the evidence of showing that a difference in the disclosure justified the difference in prosecution. However, the examiner cannot simply ignore the evidence.

The following cases illustrate the relevance of prior patents:

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past

practice of office in accepting definiteness of "fingerprint" claims);

In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

The purpose of the patent system is to encourage innovation. The claims are a means of defining the invention in such a manner that it is reasonably clear what has been patented. It is one thing to reject a claim because it covers subject matter which is disclosed or suggested by the prior art, or which is not enabled. It is quite another to reject it on what amounts to stylistic grounds.

The PTO and the courts have recognized the propriety of once exotic claim formats-- "Jepson" claims, "Markush" claims, "product-by-process" claims, "fingerprint" claims, and claims with "negative", "functional", or "alternative' limitations -- because they have realized that public policy demands that inventors not be hindered by hypertechnical claim drafting rules from fully protecting novel, nonobvious, and adequately disclosed inventions.

The instant "kit" claims are a case in point. Applicant has discovered that immunization can --depending on timing - either increase or decrease the incidence or severity of chronic immune-mediated disorders such as diabetes and SLE. A traditional product claim does not sufficiently protect applicant, as it cannot cover a prior art vaccine, even if that vaccine were used without consideration of its effect on a chronic immune-mediated disorder.

For a method claim to protect the invention, it must be crafted to avoid any instance in which the prior art use of a vaccine to immunize against an infectious disease might inherently (although inadvertently) have had the effect of also reducing the incidence or severity of a chronic immune-mediated disorder, as otherwise it could be held invalid on the ground of "inherent anticipation". Applicant has studied the literature, and has attempted to phrase the claim so as to avoid inherent anticipation, but simply cannot be sure that all such art has been avoided. An early immunization protocol might be set forth in an old or obscure journal anywhere in the world, or might have been used "publicly", without formal publication, in the United States. Indeed, the specification at page 31, lines 9-18 expressly recognizes the problem:

> The inventor appreciates that it is conceivable that a prior experimenter has, without recognition of its anti-chronic immune-mediated disorder activity, proposed or even practiced an immunization schedule

> which falls within the present disclosure, If, under the applicable law, such a proposal or practice would be deemed to anticipate or render obvious an invention here claimed, then it is within the inventor's contemplation to excise from the invention the specific embodiment in question, preserving to the maximum degree permitted by law the scope of protection originally sought.

A second problem with method claim protection is that it is geared to use of immunogens to decrease the incidence or severity of a chronic immune-mediated disorder. However, the Applicant has also enriched the art by teaching it to examine the chronic immune effects of conventional immunization. A vaccine manufacturer may find, after testing inspired by Applicant, that early immunization, while less likely to elicit this adverse effect, is also less effective against the infectious disease, and therefore continue to recommend, with appropriate warnings, late immunization. A "method of reducing the incidence or severity of a chronic immune-mediated disorder" claim would not reach this practice, even though the manufacturer would clearly have benefitted from Applicants's teachings.

A third problem is that the method claims are infringed by physicians. Applicant would prefer to assert direct infringement by the manufacturer. It is easier for Applicant to monitor vaccine labeling than to identify which doctors are following the claimed early immunization strategies.

A "kit" claim, like claims 27 and 59, solve these problems, without giving Applicant control of subject matter to which he is not entitled. Claim 27 and 59 are infringed only if the immunogen is distributed or sold with labeling either giving instructions which call upon the physician to practice the invention, or warnings indicating that the manufacturer has screened the immunogen as taught by Applicant.

Claims 27 and 59 could not be inherently anticipated by the naive use of the immunogen in an early immunization schedule,

since such use, by definition, would make no reference to the effect of the immunogen on the incidence or severity of a chronic immune-mediated disorder.

Thus, we have explained why the functionality of the immunogens here should be deemed to be affected by the labelling, per Miller and Gulack. As for In re Giolito (1976), this hardly overrules the numerous post-1976 cases which have given weight to prior patents, see above.

6.2. Claim 19 has also been rejected as anticipated by Madore (OA §9), Dengrove (OA §10), Halsey (OA §11), John (OA §12), Benveniste & LaCrange (OA §13).

Claim 19 is not a kit claim. It is an immunogenic composition claim, quoted below as examined:

> An immunogenic agent comprising a pediatric immunogen and a non-pediatric immunogen, wherein the non-pediatric immunogen is selected from the group consisting of anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, pneumonia, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens and a molecule that cross reacts immunologically to at least one of said immunogens.

Thus, to anticipate claim 19, the reference must disclose, in a single composition, both (1) a pediatric immunogen and (2) a non-pediatric immunogen.

The immunogens taught by the references are set forth below.

Madore: Haemophilus influenza B

Dengrove:	diphtheria, tetanus, pertussis
John:	oral poliovirus
Halsey:	oral poliovirus
	DPT
Benveniste:	see below

According to page 35, lines 20-26 of the specification:

> Immunogens of the present invention may be pediatric or nonpediatric immunogens. The term "pediatric immunogens" refers to immunogens that after birth were routinely administered to children less than 16 weeks old, in modern developed nations of moderate latitudes in 1992. These agents include but are not limited to BCG, measles, mumps, rubella, diphtheria, pertussis, hemophilus influenza, tetanus, hepatitis B, and polio. [emphasis added]

Madore, Dengrove, John and Halsey's immunogens are all explicitly identified as pediatric immunogens. None of these were combined with any non-pediatric immunogen.

Finally, the Examiner cites Benveniste and Lagrange. These are, respectively, pp. 346-64 and 465-502 of Bach, Immunology (2d ed. 1982).

Benveniste discusses separate compositions of the following immunogens:

horse serum (p. 47)
pollen allergens (p. 351)
house dust allergens (p. 351-2)
ingested allergens (p. 352)
drug allergens (p. 352)

We agree that none of these are "pediatric immunogens". However, even if each qualifies as a "non-pediatric immunogen", the fact remains that none was combined with a pediatric immunogen into a composition that could anticipate claim 19.

Lagrange discusses, in a general way, the various immune

responses to infections by infectious agents (bacteria, viruses, and parasites). However, it is not until page 495 that Lagrange addresses active immunization. In Table 165 he lists "principal vaccines". However, these vaccines are listed as if monovalent, and hence cannot anticipate the claimed multivalent composition.

Claim 19 has been amended to require that the composition be "pharmaceutically acceptable". Thus it cannot read inherently on, e.g., a soli sample containing both tetanus and non-tetanus bacteria.

In addition, it has been amended to require that the pediatric immunogen and the non-pediatric immunogen come from different pathogens.

6.3. Method claims 6, 32 and 33 have been rejected as anticipated by Dengrove (OA §10), Halsey (OA §11), and John (OA §12).

These claims were first rejected October 2, 1998, as anticipated by Madore, Dengrove, Halsey and John. Claim 32 was amended March 25, 1999, but the May 4, 1999 office action maintained the rejection "because the amendment of claim 32 introduces new matter".

We pointed out in our September 7, 1999 amendment, at pp. 1-2, that this holding violated MPEP §706.03(o), and in particular the "Examiner's note" on page 700-38: as to any prior art issue, "the new matter must be considered part of the claimed subject matter and cannot be ignored".

In the office action, September 29, 1999, page 5, the Examiner stated:

> The rejection of claims 6, 21, 32, 33, and 101 (method claims) under 34 U.S.C. 102(b) as being anticipated by Madore et al. is withdrawn. Applicant's arguments were persuasive.

Now, without explanation, the Examiner has reinstated three of the anticipation rejections of claims 6, 32 and 33. We hope

that this was simply an oversight on the Examiner's part. We call to the Examiner's attention MPEP §2163.06(I) ("Treatment of New Matter"): "The examiner should still consider the subject matter added to the claim in making rejections based on prior art since the new matter rejection may be overcome by applicant".

7. Miscellaneous

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Enclosures
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-Classen and Classen
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please cancel claims 69, 70, 75, 76 and 89.

Claims 5, 19, 30, 32, 38, 40, 56, 67, 69-71, 73 and 75-77 have been amended as follows:

5 (amended). The kit of claim 59 wherein one immunogen [other than] is provided which is not any of the following immunogens: a BCG, *Hemophilus influenzae*, *Streptococcus pneumoniae*, or *Neisseria* immunogen, or an immunogen of an organism which causes diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B, [hemophilus influenza,] measles, mumps [and], rubella, influenza, cholera, plague, [pneumococcus, neisseria,] varicella, rabies, typhoid or yellow fever [immunogen is provided].

19 (amended). [An] A pharmaceutically acceptable immunogenic agent comprising [a] an immunogenically effective amount of at least one pediatric immunogen and [a] of at least one non-pediatric immunogen[, wherein the non-pediatric immunogen is selected from the group consisting of anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, pneumonia, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme disease, cholera, E. coli, shigella, leishmania, leprosy, cytomegalovirus (CMV), respiratory syncytial virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria immunogens and a molecule that cross reacts immunologically to at least one of said immunogens] where said pediatric immunogen is an immunogen of a first human pathogen, and said non-pediatric immunogen is an immunogen of a second and different human pathogen.

30 (amended). The kit of claim 16 wherein said kit contains

at least one immunogen selected from the group consisting of a *Hemophilus influenzae* immunogen, a BCG immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of diphtheria, tetanus, polio, Hepatitis B, [Hemophilus influenza b,] and pertussis[, and BCG immunogens].

32 (twice amended). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG, and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of a BCG immunogen, *Hemophilus influenzae* immunogen and an immunogen of an organism which causes a disease selected from the group consisting of diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, [hemophilus influenza,] measles, mumps and rubella [immunogens], at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less.

38 (amended). The kit of claim 59, wherein, according to said instructions, for at least one such immunogen which elicits an immune response to one of said infectious diseases, the total dosage during the first 112 days after birth is [substantially] greater than that required for immunization against the infectious disease with which it is associated.

40 (amended). The kit of claim 27 wherein according to said instructions at least one immunogen is given in two or more dosings such that the shortest interval between two successive dosings thereof is at least one and less than 28 days.

56 (amended). A method of reducing the incidence or severity of an immune disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG, where, when all of the immunogens administered are selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of diphtheria, tetanus, [whole cell] pertussis, polio, hepatitis B, [hemophilus influenza,] measles, mumps and rubella [immunogens], at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on

at least three different dates, and the maximum interval between administrations is about two weeks, or less, and
where one or more immunogens are administered on at least four different dates.

67 (amended). The kit of claim 66 where said pediatric immunogen is selected from the group consisting of a BCG, immunogen, a *Hemophilus influenzae* immunogen, and an immunogen which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, [hemophilus influenza,] tetanus, hepatitis B, and polio [immunogens].

71 (amended). The kit of claim 43 in which at least one immunogen is selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, tetanus, pertussis, diphtheria, BCG, hemophilus influenza and smallpox [immunogens].

73 (amended). The kit of claim 72 where said pediatric immunogen is selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, and an immunogen which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, [hemophilus influenza,] tetanus, hepatitis B, and polio [immunogens].

77 (amended). The kit of claim 16 wherein at least one immunogen is selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, tetanus, pertussis, diphtheria, [BCG, hemophilus influenza] and smallpox [immunogens].

129 (amended). [In a] A method of protecting against an infectious disease which comprises providing a vaccine kit according to claim 59 comprising one or more immunogens protective against said disease, and instructions setting forth at least one immunization schedule for administering said

immunogens, which, if followed, results in protection against such disease, said instructions stating that one or more immunogens can be administered according to more than one immunization schedule

and warning that administration according to different immunization schedules may have different effects on the incidence of a chronic immune mediated disorder;

so that adhering to said warnings in said instructions may lead to a lower incidence of said chronic immune mediated disorder.

Please add the following new claims:

144 (new). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

wherein at least one immunogen is provided which is not any of the following immunogens: a BCG, a *Hemophilus influenzae, Streptococcus pneumoniae* or *Neisseria* immunogen, or an immunogen of an organism which causes diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B, measles, mumps, rubella, influenza, cholera, plague, varicella, rabies, typhoid or yellow fever.

145 (new). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according

to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

wherein at least one immunogen is administered on at least four different dates prior to 42 days after birth.

146 (new). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

wherein for at least one such immunogen, the total dosage during the first 112 days after birth is greater than that required for immunization against the infectious disease with which it is associated.

147 (new). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune

response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

wherein at least one immunogen so administered is one other than pertussis, and a plurality of doses of that immunogen are administered.

148 (new). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered before the mammal's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days after birth in a mouse or rat,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG, and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth,

or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less.

149 (new). The kit of claim 68 in which said nonpediatric immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, encephalitis, meningitis, typhus, typhoid fever, Lyme disease, cholera, leprosy, varicella, dengue, influenza, herpes, rabies, toxoplasmosis, coccidiomycosis, schistosomiasis and malaria, and

(b) an immunogen selected from the group consisting of *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA NonB hepatitis virus, and flavivirus immunogens.

150 (new). The kit of claim 74 in which said nonpediatric immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, encephalitis, meningitis, typhus, typhoid fever, Lyme disease, cholera, leprosy, varicella, dengue, influenza, herpes, rabies, toxoplasmosis, coccidiomycosis, schistosomiasis and malaria, and

(b) an immunogen selected from the group consisting of *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA NonB hepatitis virus, and flavivirus immunogens.

151 (new). The kit of claim 43 in which at least one immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhus, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, and

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza,* hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

152. The kit of claim 16 in which at least one immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhu, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, and

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza,* hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.